REMARKS

The undersigned attorney would like to thank Examiner Timothy Betton and Examiner Shengjun Wang for the courtesy of a telephonic interview on January 22, 2009. During the interview, the claims were discussed in view of the art cited in the Office action. The substance of the interview is incorporated in this response.

Claims 53-67 and 70-72 presently are pending and under consideration. The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejection of Claims 53-59, 62-67, 70, and 71 Under 35 U.S.C. § 103(a)

According to pages 3-7 of the outstanding Office action, claims 53-59 and 62-67, 70, and 71 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,437,267 to Weinstein *et al.* (hereinafter "Weinstein") and Published U.S. Patent Application Publication No. US 2001/0004644 A1 to Levin (hereinafter "Levin") in view of Ward-Smith in Nasal Spray Testing, Pharmaceutical Technology Europe (2002) pages 1-9 (hereinafter "Ward-Smith"). In addition, it appears that the Office also relied upon certain product information for Stadol NS®.

The Office relies on Weinstein as teaching "a device for the intranasal delivery of a medicament regimen to the nasal membranes" and relies on Levin as teaching "methods comprising intranasally administering…a local anesthetic." Office action page 5. The Office action cites Levin as disclosing "butorphanol tartrate for use in [an] intranasal device." *Id.* The Office acknowledges, however, that neither Weinstein nor Levin provide a description of spray plume actuation or volume median measurements in terms of Dv parameters. *Id.* Indeed, Weinstein provides no teaching whatsoever on spray plume geometry, or how spray plumes can have widely different features that have a profound effect on the pharmacokinetics of drug delivery.

The Office relies on Ward-Smith for teaching measurement of spray plumes using a laser diffraction measuring device. Office action pages 6-7. In particular, the Office cites Ward-Smith as characterizing spray plumes in terms of Dv10, Dv50, and Dv90 parameters,

and refers to spray plume data in Ward-Smith obtained by actuating "Pump A" or "Pump B" containing an isotonic saline solution. Office action pages 6-7; Ward-Smith pages 3-8. Then, the Office alleges that it would have been obvious to modify the spray device in Weinstein and Levin. Office action page 7.

As discussed during the telephone interview on January 22, 2009, Ward-Smith describes procedures for measuring spray plumes using a Spraytec measuring device. To illustrate the procedures described for measuring spray plumes, Ward-Smith describes, on pages 5-9, an example where spray plume parameters were measured for "Pump A" and "Pump B" following actuation of the pumps containing an isotonic saline solution. Ward-Smith provides no further identification, such as manufacturer, model number, etc., of the pumps used in the experiment. Moreover, Ward-Smith provides no description of the design parameters of the pumps giving rise to the spray plumes characterized in the example. As such, even if the skilled artisan were motivated to try the spray pumps used in Ward-Smith, Ward-Smith does not provide sufficient information to identify the spray pumps.

Applicant respectfully submits that the teachings of Weinstein, Levin, and Ward-Smith do not render obvious the subject matter of claim 53 (reproduced below), when *taken as a whole*.

> 53. An intranasal unit-dose delivery device comprising one or more sealed vessels containing a sterilized, preservative-free pharmaceutical composition, said composition comprising an effective amount of an opioid and a liquid nasal carrier, wherein upon positioning the device 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, the spray plume has a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm.

In particular, Applicant submits that the references applied by the Office action neither teach nor describe how to make the particular intranasal opioid-containing unit-dose delivery device as claimed herein that produces a spray plume having the claimed spray characteristics, which as identified by the Applicant, provide unexpectedly better drug delivery. For example, neither Weinstein nor Levin provide a description of spray plume actuation or volume median measurements. Ward-Smith provides procedures for measuring spray plumes, but does not identify the manufacturer, model, or design parameters of the

spray pumps used (i.e., "Pump A" and "Pump B"). Moreover, none of Weinstein, Levin, or Ward-Smith suggest the desirability of the particular spray plume specified in claim 53 for the claimed intranasal unit-dose delivery device for intranasal delivery of an opioid.

As discussed during the telephone interview on January 22, 2009, spray plume geometry is an important feature that impacts how quickly and how much of the therapeutic agent is absorbed through the nasal mucosa following intranasal administration using a unit-dose delivery device. Also, spray plumes can have widely different features, e.g., differences in the droplet size at specific distances from the end of the spray nozzle, and differences in the width (i.e., the span) of the spray plume as it advances from the end of the spray nozzle. Each of these features have a profound effect on the pharmacokinetics of drug delivery.

Applicant has discovered that the particular plume geometry claimed has an important and beneficial effect on the intranasal administration of an opioid containing composition. In particular, as illustrated in Figure 1 of the application, this particular spray plume provides an unexpectedly higher butorphanol concentration in the blood plasma relative to the prior art, multi-dose device. Applicant respectfully submits that the skilled artisan, based on the teachings of the applied references, would have had no reason whatsoever to believe that using a spray plume with such features could provide unexpectedly higher butorphanol concentrations in the blood plasma relative to the prior art, multi-dose device. Indeed, none of Weinstein, Levin, or Ward-Smith provide any suggestion to select, for intranasal delivery of an opioid, a spray plume having a "Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm" from the multitude of potential spray plumes.

Applicant submits, therefore, that the skilled artisan would have had no reason to produce a spray plume as defined by the claims of the instant invention. Furthermore, even if so motivated, Applicant believes that the skilled artisan would have no reasonable expectation of being able to successfully make the subject matter encompassed by claim 53 or as further specified in claims depending thereon.

Claims 54-59, 62-67, 70, and 71, depend from 53 and, therefore, incorporate all the limitations of claim 53. In view of the remarks relating to claim 53, Applicant respectfully requests that the rejection of claims 54-59, 62-67, 70, and 71 also be reconsidered and withdrawn.

Rejection of Claims 60, 61 and 72 Under 35 U.S.C. § 103(a)

According to pages 7-12 of the outstanding Office action, claims 60, 61 and 72 stand rejected under 35 U.S.C. § 103(a). Applicant understands claims 60, 61, and 72 to be rejected as obvious over Illum *et al.* in J. Pharmacol. Exp. Therapeutics (2001) 301: 391-400 (hereinafter "Illum"), Pezron *et al.* in (Expert Opin. Ther. Patents (2002) 12: 331-340 (hereinafter "Pezron"), and Mansjushree *et al.* in Can. J. Anesth. (2002) 49: 190-193 (hereinafter "Mansjushree") in view of U.S. Patent No. 6,127,385 to Midha *et al.* (hereinafter "Midha"). Applicant respectfully traverses the rejection.

Claims 60, 61 and 72 depend from and, therefore, incorporate all the limitations of independent claim 53. The arguments relating to claim 53 are reiterated here. Applicant submits that the applied references fail to teach or suggest the subject matter of claim 53, taken as a whole. As a result, Applicant respectfully requests that the rejection of claims 60, 61, and 72, which incorporate all the limitations of claim 53, be reconsidered and withdrawn.

CONCLUSION

Applicant believes that all rejections have been addressed, and early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

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